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TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	5	MAR 02	GBFULL: New full-text patent database on STN
NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	20	JUN 13	RUSSIAPAT: New full-text patent database on STN
NEWS	21	JUN 13	FRFULL enhanced with patent drawing images
NEWS	22	JUN 27	MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS	23	JUL 01	MEDICONF removed from STN
NEWS	24	JUL 07	STN Patent Forums to be held in July 2005
NEWS	25	JUL 13	SCISEARCH reloaded
NEWS	26	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available

NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that

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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

*ENCOMPPAT - EnCompass Patent File 1964-present (Supporters)
*ENCOMPPAT2 - EnCompass Patent File 1964-Present (Non-Supporters)

* The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

FILE LAST UPDATED: 23 JUL 2005 (20050723/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s WNT
          3897 WNT
           336 WNTS
L1        3942 WNT
               (WNT OR WNTS)

=> s l1 (S) antagon?
        518406 ANTAGON?
L2         244 L1 (S) ANTAGON?

=> s osteo? or bone
        211167 OSTEO?
        424243 BONE
         91740 BONES
        446342 BONE
               (BONE OR BONES)
L3      553450 OSTEO? OR BONE

=> s l3 and l2
L4           70 L3 AND L2
```

```
=> s multiple myeloma
        445180 MULTIPLE
          3940 MULTIPLES
        446855 MULTIPLE
                 (MULTIPLE OR MULTIPLES)
         30767 MYELOMA
           763 MYELOMAS
         31029 MYELOMA
                 (MYELOMA OR MYELOMAS)
L5       22597 MULTIPLE MYELOMA
                 (MULTIPLE(W)MYELOMA)

=> s l5 and l4
L6           1 L5 AND L4

=> d ibib 1

L6   ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:    2003612654     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 14695408
TITLE:               The role of the Wnt-signaling antagonist
                     DKK1 in the development of osteolytic lesions in
                     multiple myeloma.
COMMENT:             Comment in: N Engl J Med. 2003 Dec 25;349(26):2479-80.
                     PubMed ID: 14695406
                     Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                     reply 1464-6. PubMed ID: 15070800
                     Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                     reply 1464-6. PubMed ID: 15074002
                     Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                     reply 1464-6. PubMed ID: 15074001
                     Comment in: N Engl J Med. 2004 Jul 8;351(2):197-8. PubMed
                     ID: 15247367
AUTHOR:              Tian Erming; Zhan Fenghuang; Walker Ronald; Rasmussen Erik;
                     Ma Yupo; Barlogie Bart; Shaughnessy John D Jr
CORPORATE SOURCE:    Donna D. and Donald M. Lambert Laboratory of Myeloma
                     Genetics, Myeloma Institute for Research and Therapy,
                     College of Medicine, University of Arkansas for Medical
                     Sciences, Little Rock 72205, USA.
CONTRACT NUMBER:     CA55819 (NCI)
     CA97513 (NCI)
SOURCE:              New England journal of medicine, (2003 Dec 25) 349 (26)
                     2483-94.
                     Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200401
ENTRY DATE:          Entered STN: 20031230
                     Last Updated on STN: 20040107
                     Entered Medline: 20040106


=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1           3942 S WNT
L2            244 S L1 (S) ANTAGON?
L3         553450 S OSTEO? OR BONE
L4             70 S L3 AND L2
L5          22597 S MULTIPLE MYELOMA
```

```
L6            1 S L5 AND L4

=> s l2 and l5
L7            1 L2 AND L5

=> s myeloma
         30767 MYELOMA
           763 MYELOMAS
L8       31029 MYELOMA
                 (MYELOMA OR MYELOMAS)

=> s l8 and l2
L9            1 L8 AND L2

=> s l1 and l3
L10         451 L1 AND L3

=> s l10 and l5
L11           7 L10 AND L5

=> s l11 not py>2002
       1489868 PY>2002
L12           1 L11 NOT PY>2002

=> d ibib

L12  ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:   2001420323     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11468178
TITLE:              Identifying intercellular signaling genes expressed in
                    malignant plasma cells by using complementary DNA arrays.
AUTHOR:             De Vos J; Couderc G; Tarte K; Jourdan M; Requirand G;
                    Delteil M C; Rossi J F; Mechti N; Klein B
CORPORATE SOURCE:   INSERM U475, Unit for Cellular Therapy, CHU Montpellier, 99
                    Rue Puech Villa, 34197 Montpellier Cedex 5, France.
SOURCE:             Blood, (2001 Aug 1) 98 (3) 771-80.
                    Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200109
ENTRY DATE:         Entered STN: 20010917
                    Last Updated on STN: 20010917
                    Entered Medline: 20010913


=> d kwic

L12  ANSWER 1 OF 1     MEDLINE on STN
AB   In multiple myeloma (MM), the growth of primary plasma
     cells depends not only on interleukin-6 (IL-6), but also on additional
     unidentified signals delivered by the bone marrow environment.
     Using Atlas complementary DNA (cDNA) arrays comprising 268 genes coding
     for intercellular signaling molecules, this study identified genes.  .  .
     receptor (TR) that is linked to HB-EGF and syndecan-1 processing and to
     cell invasion, chemokine receptors CCR1 and CCR2, the Wnt
     pathway actor Frizzled-related protein (FRZB), and the Notch receptor
     ligand Jagged 2.  These data, obtained with the Atlas cDNA array,.  .  .
CT    B-Lymphocytes: ME, metabolism
      Cell Division: DE, drug effects
      Epidermal Growth Factor: ME, metabolism
      Flow Cytometry
      Gene Expression: GE, genetics
```

```
      Humans
        Multiple Myeloma: GE, genetics
       *Multiple Myeloma: ME, metabolism
        Multiple Myeloma: PA, pathology
      Neoplasm Proteins: GE, genetics
      Neoplasm Proteins: ME, metabolism
     *Oligonucleotide Array Sequence Analysis: MT, methods
     *Plasma Cells:.  .  .


=> s (dickkopf () 1) or (DKK () 1)
             85 DICKKOPF
              8 DICKKOPFS
             90 DICKKOPF
                  (DICKKOPF OR DICKKOPFS)
        3513889 1
             49 DICKKOPF (W) 1
            119 DKK
              9 DKKS
            121 DKK
                  (DKK OR DKKS)
        3513889 1
             44 DKK (W) 1
L13          70 (DICKKOPF (W) 1) OR (DKK (W) 1)

=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1         3942 S WNT
L2          244 S L1 (S) ANTAGON?
L3       553450 S OSTEO? OR BONE
L4           70 S L3 AND L2
L5        22597 S MULTIPLE MYELOMA
L6            1 S L5 AND L4
L7            1 S L2 AND L5
L8        31029 S MYELOMA
L9            1 S L8 AND L2
L10         451 S L1 AND L3
L11           7 S L10 AND L5
L12           1 S L11 NOT PY>2002
L13          70 S (DICKKOPF () 1) OR (DKK () 1)

=> s l13 and l11
L14           2 L13 AND L11

=> d ibib 1-2

L14  ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:   2005314981     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 15965110
TITLE:              How wnt signaling affects bone repair
                    by mesenchymal stem cells from the bone marrow.
AUTHOR:             Gregory Carl A; Gunn William G; Reyes Emigdio; Smolarz
                    Angela J; Munoz James; Spees Jeffrey L; Prockop Darwin J
CORPORATE SOURCE:   Center for Gene Therapy, Tulane University Health Sciences
                    Center, 1430 Tulane Avenue, New Orleans, LA 70112..
                    ca_gregory@hotmail.com
SOURCE:             Annals of the New York Academy of Sciences, (2005 May) 1049
                    97-106.
                    Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
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LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20050621
Last Updated on STN: 20050621

L14 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2003612654 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14695408
TITLE: The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma.
COMMENT: Comment in: N Engl J Med. 2003 Dec 25;349(26):2479-80. PubMed ID: 14695406
Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author reply 1464-6. PubMed ID: 15070800
Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author reply 1464-6. PubMed ID: 15074002
Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author reply 1464-6. PubMed ID: 15074001
Comment in: N Engl J Med. 2004 Jul 8;351(2):197-8. PubMed ID: 15247367
AUTHOR: Tian Erming; Zhan Fenghuang; Walker Ronald; Rasmussen Erik; Ma Yupo; Barlogie Bart; Shaughnessy John D Jr
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics, Myeloma Institute for Research and Therapy, College of Medicine, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
CONTRACT NUMBER: CA55819 (NCI)
CA97513 (NCI)
SOURCE: New England journal of medicine, (2003 Dec 25) 349 (26) 2483-94.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031230
Last Updated on STN: 20040107
Entered Medline: 20040106

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11

=> d ibib kwic l12

L12 ANSWER 1 OF 1 MEDLINE on STN
ACCESSION NUMBER: 2001420323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11468178
TITLE: Identifying intercellular signaling genes expressed in malignant plasma cells by using complementary DNA arrays.
AUTHOR: De Vos J; Couderc G; Tarte K; Jourdan M; Requirand G; Delteil M C; Rossi J F; Mechti N; Klein B
CORPORATE SOURCE: INSERM U475, Unit for Cellular Therapy, CHU Montpellier, 99 Rue Puech Villa, 34197 Montpellier Cedex 5, France.
SOURCE: Blood, (2001 Aug 1) 98 (3) 771-80.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913

AB In multiple myeloma (MM), the growth of primary plasma cells depends not only on interleukin-6 (IL-6), but also on additional unidentified signals delivered by the bone marrow environment. Using Atlas complementary DNA (cDNA) arrays comprising 268 genes coding for intercellular signaling molecules, this study identified genes. . . receptor (TR) that is linked to HB-EGF and syndecan-1 processing and to cell invasion, chemokine receptors CCR1 and CCR2, the Wnt pathway actor Frizzled-related protein (FRZB), and the Notch receptor ligand Jagged 2. These data, obtained with the Atlas cDNA array,. . .

CT B-Lymphocytes: ME, metabolism
Cell Division: DE, drug effects
Epidermal Growth Factor: ME, metabolism
Flow Cytometry
Gene Expression: GE, genetics
Humans
Multiple Myeloma: GE, genetics
*Multiple Myeloma: ME, metabolism
Multiple Myeloma: PA, pathology
Neoplasm Proteins: GE, genetics
Neoplasm Proteins: ME, metabolism
*Oligonucleotide Array Sequence Analysis: MT, methods
*Plasma Cells:. . .

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1 3942 S WNT
L2 244 S L1 (S) ANTAGON?
L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11

```
=> s l13 and l3
L15         19 L13 AND L3

=> s l15 and express?
        932565 EXPRESS?
L16         14 L15 AND EXPRESS?

=> s l16 not py>2002
       1489868 PY>2002
L17          6 L16 NOT PY>2002

=> d ibib 1-3

L17  ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002693855     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12455632
TITLE:              Bmp, Fgf and Wnt signalling in programmed cell death and
                    chondrogenesis during vertebrate limb development: the role
                    of Dickkopf-1.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Institut fur Entwicklungs- und Molekularbiologie der Tiere
                    (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SOURCE:             International journal of developmental biology, (2002) 46
                    (7) 943-7.
                    Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY:       Spain
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200306
ENTRY DATE:         Entered STN: 20021214
                    Last Updated on STN: 20030619
                    Entered Medline: 20030618

L17  ANSWER 2 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002280313     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12021176
TITLE:              Global gene profiling in human endometrium during the
                    window of implantation.
AUTHOR:             Kao L C; Tulac S; Lobo S; Imani B; Yang J P; Germeyer A;
                    Osteen K; Taylor R N; Lessey B A; Giudice L C
CORPORATE SOURCE:   Department of Gynecology and Obstetrics, Stanford
                    University, Stanford, California 94305, USA.
CONTRACT NUMBER:    U54 HD31398 (NICHD)
SOURCE:             Endocrinology, (2002 Jun) 143 (6) 2119-38.
                    Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200206
ENTRY DATE:         Entered STN: 20020522
                    Last Updated on STN: 20020619
                    Entered Medline: 20020618

L17  ANSWER 3 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002131765     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11867524
TITLE:              The Wnt antagonist Dickkopf-1 is
                    regulated by Bmp signaling and c-Jun and modulates
                    programmed cell death.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Entwicklungs- und Molekularbiologie der Tiere,
                    Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany..
```

lars.grotewold@uni-duesseldorf.de
SOURCE: EMBO journal, (2002 Mar 1) 21 (5) 966-75.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

=> d ibib 4-6

L17 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001447406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291860
TITLE: The role of the homeodomain protein Bozozok in zebrafish axis formation.
AUTHOR: Solnica-Krezel L; Driever W
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SOURCE: International journal of developmental biology, (2001) 45 (1) 299-310.
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L17 ANSWER 5 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

L17 ANSWER 6 OF 6 MEDLINE on STN
ACCESSION NUMBER: 1999425169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10495270
TITLE: Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AUTHOR: Monaghan A P; Kioschis P; Wu W; Zuniga A; Bock D; Poustka A; Delius H; Niehrs C
CORPORATE SOURCE: Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120,

Heidelberg, Germany.
SOURCE: Mechanisms of development, (1999 Sep) 87 (1-2) 45-56.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ243963; GENBANK-AJ243964
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

=> d kwic 6

L17 ANSWER 6 OF 6 MEDLINE on STN
TI Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AB Dickkopf-1 (dkk-1) is member of a novel family of secreted proteins and functions in head induction during Xenopus embryogenesis, acting as a. . . of two additional murine members of the dkk family, dkk-2 and dkk-3; and (2) analysis of adult and embryonic gene expression of mouse dkk-1,-2, and -3, Xenopus dkk-1 as well as chicken dkk-3. Comparative developmental analyses of the dkk-1, dkk-2 and dkk-3 in mice indicate that these genes are both temporally and spatially regulated. They define overlapping deep domains in mesenchymal lineages suggesting a co-ordinated mode of action. All dkks show distinct and elevated expression patterns in tissues that mediate epithelial- mesenchyme transformations suggesting that they may participate in heart, tooth, hair and whisker follicle, limb and bone induction. In the limb buds expression of these genes are found in regions of programmed cell death. In a given organ, dkk-1 tends to be the earliest member expressed . Comparison with Xenopus dkk-1 and chicken dkk-3 shows evolutionarily conserved expression patterns. Our observations indicate that dkk genes constitute a new family of secreted proteins that may mediate inductive interactions between. . .
CT Amino Acid Sequence
Animals
Ectoderm: ME, metabolism
Epithelial Cells: ME, metabolism
*Gene Expression Regulation, Developmental
In Situ Hybridization
*Mesoderm: ME, metabolism
Mice
Molecular Sequence Data
*Proteins: GE, genetics
*Proteins: ME, metabolism
Reverse. . .

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.44	5.65

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

FILE COVERS 1907 - 25 Jul 2005 VOL 143 ISS 5
FILE LAST UPDATED: 24 Jul 2005 (20050724/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s WNT
          4331 WNT
           330 WNTS
L18       4365 WNT
                (WNT OR WNTS)

=> s l1 (S) antagon?
          4331 WNT
           330 WNTS
          4365 WNT
                (WNT OR WNTS)
        270850 ANTAGON?
L19        273 L1 (S) ANTAGON?

=> s l18 (S) antagon?
        270850 ANTAGON?
L20        273 L18 (S) ANTAGON?

=> s myeloma
         16718 MYELOMA
           557 MYELOMAS
L21      16913 MYELOMA
                (MYELOMA OR MYELOMAS)

=> s l20 and l21
L22           5 L20 AND L21

=> d ibib 1-3

L22  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:450819  CAPLUS
DOCUMENT NUMBER:          142:461611
TITLE:                    Diagnosis, prognosis and identification of potential
                          therapeutic targets of multiple myeloma
                          based on gene expression profiling
INVENTOR(S):              Shaughnessy, John D.; Barlogie, Bart; Zhan, Fenghuang
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S.
                          Ser. No. 454,263.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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US 2005112630	A1	20050526	US 2004-931780		20040901
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
US 2004009523	A1	20040115	US 2003-454263		20030604
PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
			US 2002-355386P	P	20020208
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			US 2002-289746	A2	20021107
			US 2003-409004	A2	20030408
			US 2003-454263	A2	20030604

L22 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:992468 CAPLUS
DOCUMENT NUMBER: 142:371352
TITLE: Wnt signaling antagonist DKK1 in the development of osteolytic lesion in multiple myeloma
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Institute of Clinical Endocrinology, Tokyo Women≈s Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 49(2), 166-170
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L22 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:515641 CAPLUS
DOCUMENT NUMBER: 141:52350
TITLE: Expression of genes DKK1 and FRZB as molecular determinants of myeloma bone disease and transcription regulation for treatment thereof
INVENTOR(S): Shaughnessy, John D.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004053063	A2	20040624	WO 2003-US38372		20031204
WO 2004053063	A3	20041125			
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004137489	A1	20040715	US 2003-727461		20031204
PRIORITY APPLN. INFO.:			US 2002-431040P	P	20021205

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L22 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:40999 CAPLUS
DOCUMENT NUMBER: 140:109553
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Zhan, Fenghuang; Barlogie, Bart
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 67 pp., Cont.-in-part of U.S. Ser. No. 409,004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004009523	A1	20040115	US 2003-454263		20030604
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
US 2005112630	A1	20050526	US 2004-931780		20040901
PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
			US 2002-355386P	P	20020208
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			US 2003-409004	A2	20030408
			US 2003-454263	A2	20030604

L22 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1011522 CAPLUS
DOCUMENT NUMBER: 140:126264
TITLE: The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma
AUTHOR(S): Tian, Erming; Zhan, Fenghuang; Walker, Ronald; Rasmussen, Erik; Ma, Yupo; Barlogie, Bart; Shaughnessy, John D., Jr.
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics, Myeloma Institute for Research and Therapy, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
SOURCE: New England Journal of Medicine (2003), 349(26), 2483-2494
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s (dickkopf () 1) or (DKK () 1)
           175 DICKKOPF
             8 DICKKOPFS
           177 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
       8339167 1
           104 DICKKOPF (W) 1
           123 DKK
            11 DKKS
           124 DKK
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            58 DKK (W) 1
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              8 DICKKOPFS
            177 DICKKOPF
                  (DICKKOPF OR DICKKOPFS)
        8339167 1
            104 DICKKOPF-1
                  (DICKKOPF(W)1)
             98 DKK1
L24         155 DICKKOPF-1 OR DKK1

=> s l23 or l24
L25         170 L23 OR L24

=> s osteo?
L26       61795 OSTEO?

=> s l26 and l25
L27          32 L26 AND L25

=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1          3942 S WNT
L2           244 S L1 (S) ANTAGON?
L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11
L15           19 S L13 AND L3
L16           14 S L15 AND EXPRESS?
L17            6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18         4365 S WNT
L19          273 S L1 (S) ANTAGON?
L20          273 S L18 (S) ANTAGON?
L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25

=> s l27 and l21
L28            7 L27 AND L21

=> d ibib 1-4

L28  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:450819  CAPLUS
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DOCUMENT NUMBER: 142:461611
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Barlogie, Bart; Zhan, Fenghuang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S. Ser. No. 454,263.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005112630	A1	20050526	US 2004-931780		20040901
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
US 2004009523	A1	20040115	US 2003-454263		20030604
PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
			US 2002-355386P	P	20020208
			US 2002-403075P	P	20020813
			US 2002-289746	A2	20021107
			US 2003-409004	A2	20030408
			US 2003-454263	A2	20030604

L28 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:348815 CAPLUS
DOCUMENT NUMBER: 142:397651
TITLE: Inhibitors of protein Dickkopf-1 for treating osteolytic lesions in multiple myeloma and enhancing osteogenesis
INVENTOR(S): Prockop, Darwin; Gregory, Carl; Gunn, William
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 84 pp., Cont.-in-part of U.S. Ser. No. 830,352, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005084494	A1	20050421	US 2004-839515		20040505
US 2004235166	A1	20041125	US 2003-442506		20030521
PRIORITY APPLN. INFO.:			US 2003-442506	A2	20030521
			US 2004-830352	B2	20040422

L28 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:992468 CAPLUS
DOCUMENT NUMBER: 142:371352
TITLE: Wnt signaling antagonist DKK1 in the development of osteolytic lesion in multiple myeloma
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Institute of Clinical Endocrinology, Tokyo Women≈s Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 49(2), 166-170
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

L28 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:515641 CAPLUS
DOCUMENT NUMBER: 141:52350
TITLE: Expression of genes DKK1 and FRZB as molecular determinants of myeloma bone disease and transcription regulation for treatment thereof
INVENTOR(S): Shaughnessy, John D.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004053063	A2	20040624	WO 2003-US38372	20031204
WO 2004053063	A3	20041125		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004137489	A1	20040715	US 2003-727461	20031204
PRIORITY APPLN. INFO.:			US 2002-431040P	P 20021205

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L28 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:504577 CAPLUS
DOCUMENT NUMBER: 141:219048
TITLE: Activation mechanism of osteoclasts
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Dep. of Medicine II, Tokyo Women's Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 48(3), 274-280
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L28 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:40999 CAPLUS
DOCUMENT NUMBER: 140:109553
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Zhan, Fenghuang; Barlogie, Bart
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 67 pp., Cont.-in-part of U.S. Ser. No. 409,004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004009523	A1	20040115	US 2003-454263		20030604
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
US 2005112630	A1	20050526	US 2004-931780		20040901
PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
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			US 2003-409004	A2	20030408
			US 2003-454263	A2	20030604

L28 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1011522 CAPLUS
DOCUMENT NUMBER: 140:126264
TITLE: The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma
AUTHOR(S): Tian, Erming; Zhan, Fenghuang; Walker, Ronald; Rasmussen, Erik; Ma, Yupo; Barlogie, Bart; Shaughnessy, John D., Jr.
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics, Myeloma Institute for Research and Therapy, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
SOURCE: New England Journal of Medicine (2003), 349(26), 2483-2494
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	40.47	46.12

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FILE LAST UPDATED: 19 JUL 2005 <20050719/UP>
MOST RECENT UPDATE WEEK: 200528 <200528/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s WNT
1265 WNT
148 WNTS
L29 1307 WNT
(WNT OR WNTS)

=> s l29 (s) antag?
48582 ANTAG?
L30 161 L29 (S) ANTAG?

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        920163 1
            20 DICKKOPF (W) 1
           178 DKK
            16 DKKS
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        920163 1
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L31         46 (DICKKOPF (W) 1) OR (DKK (W) 1)

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             4 DICKKOPFS
           107 DICKKOPF
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        920163 1
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                 (DICKKOPF(W)1)
            26 DKK1
           178 DKK
            16 DKKS
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L32         62 DICKKOPF-1 OR DKK1 OR DKK-1

=> s l32 or l31
L33         62 L32 OR L31

=> s osteo?
L34      27031 OSTEO?

=> s l34 or bone
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          8795 BONES
         50481 BONE
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L35      59451 L34 OR BONE

=> s cancer? or tumor? or neoplas?
         70033 CANCER?
         58772 TUMOR?
         20120 NEOPLAS?
L36      87552 CANCER? OR TUMOR? OR NEOPLAS?

=> s myeloma
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          1344 MYELOMAS
L37      14570 MYELOMA
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=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1        3942 S WNT
L2         244 S L1 (S) ANTAGON?
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L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
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L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
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L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11
L15           19 S L13 AND L3
L16           14 S L15 AND EXPRESS?
L17            6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18         4365 S WNT
L19          273 S L1 (S) ANTAGON?
L20          273 S L18 (S) ANTAGON?
L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29         1307 S WNT
L30          161 S L29 (S) ANTAG?
L31           46 S (DICKKOPF () 1) OR (DKK () 1)
L32           62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33           62 S L32 OR L31
L34        27031 S OSTEO?
L35        59451 S L34 OR BONE
L36        87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37        14570 S MYELOMA

=> s l62 and l35
L62 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l33 and l34
L38           39 L33 AND L34

=> s l38 and l37
L39           18 L38 AND L37

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        287458 PY>2002
L40            8 L39 NOT PY>2002

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         870322 1/CLM
              3 DICKKOPF-1/CLM
                  ((DICKKOPF(W)1)/CLM)
              5 DKK1/CLM
             26 DKK/CLM
         870322 1/CLM
              5 DKK-1/CLM
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                ((DKK(W)1)/CLM)
            16 DICKKOPF/CLM
        870322 1/CLM
             3 DICKKOPF/CLM (W) 1/CLM
            26 DKK/CLM
        870322 1/CLM
             5 DKK/CLM (W) 1/CLM
L41         10 ((DICKKOPF-1/CLM OR DKK1/CLM OR DKK-1/CLM) OR ((DICKKOPF/CLM
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=> s l41 and l40
L42          1 L41 AND L40

=> d ibib

L42    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2002066509 PCTFULL  ED 20020910  EW 200235
TITLE (ENGLISH):         TREATMENT INVOLVING DKK-1 OR
                         ANTAGONISTS THEREOF
TITLE (FRENCH):          TRAITEMENT FAISANT APPEL A DKK-1 OU
                         AUX ANTAGONISTES DE DKK-1
INVENTOR(S):             DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
                         San Mateo, CA 94403, US;
                         STEWART, Timothy A., 465 Douglas Street, San Francisco,
                         CA 94114, US
PATENT ASSIGNEE(S):      GENENTECH, INC., 1 DNA Way, South San Francisco, CA
                         94080, US [US, US]
AGENT:                   HASAK, Janet E.$, GENENTECH, INC., MS 49, 1 DNA Way,
                         South San Francisco, CA 94080-4990$, US
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2002066509         A2 20020829
DESIGNATED STATES
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                         CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                         IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
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       RW (ARIPO):       GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
       RW (EAPO):        AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):         AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
                         TR
       RW (OAPI):        BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 2002-US4573        A  20020215
PRIORITY INFO.:          US 2001-60/269,435       20010216


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     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1         3942 S WNT
L2          244 S L1 (S) ANTAGON?
L3       553450 S OSTEO? OR BONE
L4           70 S L3 AND L2
L5        22597 S MULTIPLE MYELOMA
L6            1 S L5 AND L4
L7            1 S L2 AND L5
L8        31029 S MYELOMA
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L9            1 S L8 AND L2
L10         451 S L1 AND L3
L11           7 S L10 AND L5
L12           1 S L11 NOT PY>2002
L13          70 S (DICKKOPF () 1) OR (DKK () 1)
L14           2 S L13 AND L11
L15          19 S L13 AND L3
L16          14 S L15 AND EXPRESS?
L17           6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18        4365 S WNT
L19         273 S L1 (S) ANTAGON?
L20         273 S L18 (S) ANTAGON?
L21       16913 S MYELOMA
L22           5 S L20 AND L21
L23         123 S (DICKKOPF () 1) OR (DKK () 1)
L24         155 S DICKKOPF-1 OR DKK1
L25         170 S L23 OR L24
L26       61795 S OSTEO?
L27          32 S L26 AND L25
L28           7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29        1307 S WNT
L30         161 S L29 (S) ANTAG?
L31          46 S (DICKKOPF () 1) OR (DKK () 1)
L32          62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33          62 S L32 OR L31
L34       27031 S OSTEO?
L35       59451 S L34 OR BONE
L36       87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37       14570 S MYELOMA
L38          39 S L33 AND L34
L39          18 S L38 AND L37
L40           8 S L39 NOT PY>2002
L41          10 S L33/CLM
L42           1 S L41 AND L40

=> s l33/ab
             5 DICKKOPF/AB
        221598 1/AB
             3 DICKKOPF-1/AB
                 ((DICKKOPF(W)1)/AB)
             1 DKK1/AB
             5 DKK/AB
        221598 1/AB
             2 DKK-1/AB
                 ((DKK(W)1)/AB)
             5 DICKKOPF/AB
        221598 1/AB
             3 DICKKOPF/AB (W) 1/AB
             5 DKK/AB
        221598 1/AB
             2 DKK/AB (W) 1/AB
L43          4 ((DICKKOPF-1/AB OR DKK1/AB OR DKK-1/AB) OR ((DICKKOPF/AB (W)
               1/AB) OR (DKK/AB (W) 1/AB)))

=> s l42 and l35
L44          1 L42 AND L35

=> d ibib

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TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
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L44 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN
TIEN TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
TIFR TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES DE DKK-1
ABEN Antagonists to Dickkopf-1 (Dkk-1) proteins are administered in effective amounts to treat disorders involving insulin resistance, such as non-insulin-dependent diabetes mellitus (NIDDM), hypoinsulinemia, and disorders involving muscle atrophy, trauma, or degeneration. Preferably, the antagonists are composed of compositions comprising antibodies directed to Dkk -1 in a pharmaceutically acceptable carrier for use in blocking the effects of Dkk-1. Additionally provided is a method of treating obesity or hyperinsulinemia in a mammal by administering an effective amount of Dkk-1 to a mammal. Also provided are methods of diagnosing insulin resistance, hyper- and hypoinsulinemia, obesity, and related disorders using Dkk-1 as a target and non-human transgenic animals that overexpress dkk-1 nucleic acid.
ABFR L'invention concerne un traitement consistant a administrer des antagonistes des proteines Dickkopf-1 (Dkk -1) en quantites efficaces pour traiter les troubles impliquant une resistance insulinique, tels que le diabete non insulino-dependant (NIDDM), l'hypoinsulinemie et les troubles impliquant une atrophie musculaire, un traumatisme ou une degeneration. Ces antagonistes sont avantageusement composes d'anticorps diriges contre Dkk-1 dans un excipient pharmaceutiquement acceptable et utilises pour bloquer les effets de Dkk-1.

L'invention concerne egalement une methode de traitement de l'obesite ou de l'hyperinsulinemie chez un mammifere, consistant a administrer une quantite efficace de Dkk-1 a un patient. L'invention concerne egalement des methodes permettant de diagnostiquer la resistance insulinique, l'hyper- et l'hypoinsulinemie, l'obesite et les troubles associes, a l'aide de Dkk-1 comme cible et des animaux transgeniques non humains surexprimant l'acide nucleique dkk-1.

DETD TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
Background of the Invention
Field of the Invention
The present invention provides for the diagnosis and treatment of disorders involving. . . hyperinsulinemia and for repairing and regenerating muscle in
mammals. More particularly, the present invention relates to the use of Dickkopf- I (Dkk- 1) protein to treat
obesity and hyperinsulinemia and to the use of antagonists that bind to Dkk- I and/or neutralize its activity. . .

Dkk-I (WO 99/46281 published Sept. 16, 1999, wherein the Dkk-1 is designated as PRO1008 and is
encoded by DNA57530; WO 00/18914 published April 6, 2000; WO 00/52047 published September 8,
2000; WO. . .
. . .
as polycystic ovarian disease, dermatological
disorders such as infections, varicose veins, Acanthosis nigricans, and eczema, exercise intolerance, insulin
resistance, hypertension, hypercholesterolernia, cholelithiasis, osteoarthritis, orthopedic injury,
thromboembolic disease, cancer, and coronary heart disease. Rissanen et al., British Medical Journal, 301.

t]
Summary of the Invention
Accordingly, antagonists to Dkk-1, such as
antibodies, are herein disclosed to be useful in the
treatment of insulin resistance associated with, for example, glucose intolerance,. . .
. . .
mammal in need thereof an
effective amount of an antagonist to Dkk Preferably, the mammal is human, the Dkk-I is human Dkk-1,
and/or the human has NIDDM. Also preferred is systemic administration. The antagonist is preferably,an
antibody that binds Dkk- 1, and more preferably a
monoclonal antibody that binds Dkk- 1, and still
more
preferably one that neutralizes an insulin-resistance or hypoinsulinernic activity of Dkk Most preferred is
a monoclonal antibody prepared from. . .

Preferably, the measuring is carried out using an anti-Dkk-1 antibody, such as a monoclonal
antibody, in an immunoassay, Also, preferably such anti-Dkk-1 antibody comprises a label, more preferably
a fluorescent label, a radioactive label, or an enzyme label, such as a bioluminescent label. . .

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Additionally provided is a monoclonal antibody preparation prepared by hyperimmunizing mice
with tagged Dkk- 1 (preferably purified recombinant

polyhistidine-tagged human Dkk-I) diluted in an
adjuvant, fusing B-cells from the mice having anti-Dkk-
1 antibody titers (preferably high titers) with mouse
myelorna cells and obtaining supernatants, harvesting the supernatants,
screening the harvested supernatants
for antibody production,. . .

. . .

a candidate pharmaceutical drucr
on insulin resistance, hypoinsulinernia, or muscle repair comprising
administering said drug to a non-human
transgenic animal that overexpresses dkk-1 nucleic
acid and determining the effect of the drug on glucose
clearance from the blood of said animal, on circulating insulin. . .
the animal is a rodent, more preferably a mouse or rat, and most
preferably a mouse. In another preferred embodiment, the dkk-
1 nucleic acid overexpressed by the animal is
under the control of a muscle-specific promoter, and the cDNA is
overexpressed in muscle. . .

(a) a container comprising an antibody that binds Dkk-1;
(b) a container comprising a standard sample containing Dkk-
1; and
(c) instructions for using the antibody and standard sample to detect
insulin resistance, hypoinsulinemia,
hyperinsulinemia, or obesity, wherein either the antibody. . . is
detectably labeled or the kit
further comprises another container comprising a second antibody that is
detectably labeled and binds to the
Dkk-1 or to the antibody that binds Dkk Preferably
the anti-Dkk-1 antibody of the kit is a monoclonal
antibody, more preferably one that neutralizes an insulin-resistance,
hyperinsulinemic, hypoinsulinemic, or
obesity activity of Dkk-1.

. . .

for detecting the presence or onset of obesity or
hyperinsulinemia in a mammal comprising the steps of-
(a) measuring the amount of Dkk-1 in a sample from
said mammal; and
(b) comparing the amount determined in step (a) to an amount of Dkk-1
present in a standard sample, a
decreased level in the amount of Dkk-1 in step (a)
being indicative of obesity or hyperinsulinemia.

Preferably, the measuring is carried out using an anti-Dkk-
1 antibody in an immunoassay. Also,
preferably the anti-Dkk- I antibody comprises a label. The preferred
labels and immunoassays are those as
6
set. . .

In a preferred embodiment the Dkk- I is human Dkk- 1
in the kit and it may further comprise a container with
a weight-loss agent.

. . .

effect of a candidate pharmaceutical drug
on obesity or hyperinsulinernia comprising administering said druo, to a
non-human binary transgenic animal
that expresses dkk-1 nucleic acid and determining
the effect of the drug on an obesity-determining property or
on the level of insulin in said. . .

The invention also provides a non-human transgenic animal that
overexpresses dkk-1 nucleic acid.

. . .

method for repairing or regenerating muscle in a mammal comprising administering to the mammal an effective amount of an antagonist to Dkk-1, preferably an antibody that binds to Dkk Preferably, the mammal is human and/or the antibody is a monoclonal antibody.

(a) a container comprising an antagonist toDkk- 1, preferably an antibody that binds Dkk- 1; and
(b) instructions for using the antagonist to repair or regenerate muscle in a mammal.

Figure 2 shows a gel of human Dkk-1 expressed in baculovirus and its clipping.

Figure 3A shows the effects of human Dkk- 1 (dark bars) on basal glucose uptake in L6 muscle cells for 2, 6, and 26 hours. Figures 3B and 3C show, respectively, the effects of human Dkk-1 on basal (light bars) and 30 nM-insulin-stimulated (dark bars) glucose uptake in L6 muscle cells.

. . .
shows the effects of human Dkk]l on basal and insulin-dependent glucose uptake (expressed as percent control) as a function of human Dkk-1 concentration (nM) upon 48-hour treatment.

Figure 5A-513 show respectively the effect of human Dkk-1 on the incorporation of glucose into glycogen in L6 muscle cells with (dark bars) and without (light bars) insulin for 48. . .

Ficrures 8A-8D show the effect of 40 nM human Dkk-1 (dark bars) on the kinase activities of PDK-I (Fig. 8A), GSK3 P (Fig. 813), S6 kinase (Fig. SC), and Akt (Fig.. . .

Figures 9A and 9B show the effect of human Dkk-1 on levels of basal (light bars) and 30 nM-insulin-stimulated (dark bars) criucose uptake of 3T3 LI cells (adipocytes) after 48-hour. . .

. . .
Dkk-I (triangles). Figure I IB shows the insulin levels in the female FVB mice intravenously injected with saline (control), 0.05 mg/kg/day human Dkk-1, and 0.2 mg/kg/day human Dkk Figure 12A shows the effects of human Dkk-1 on expression of various markers of muscle differentiation in mice injected therewith, with control (light bars) and 0.2 mg/kg/day of human. . .

Figure 17 shows the effect of an anti-human Dkk-1 monoclonal antibody on the Dkk-1-mediated decrease in glucose uptake in L6 cells in the absence and presence of insulin, where the. . . the L6 cells with 40 nM Dkk-I are black bars, and the L6 cells with 40 nM Dkk-I and 0.5 [tg/mL anti-Dkk-1 antibody are dark gray bars on the far right.

An insulin-resistance-treating agent is an agent other than an antagonist to Dkk-1 that is used to treat insulin resistance, such as, for example, hypoglycemic agents. Examples of such treating agents include insulin (one or. . .

As used herein, Dkk- I or Dickkopf- 1 refers to

Wnt inhibitor with properties and characteristics
described in WO 99/46281 published September 16, 1999 and Glinka et aL,
Nature,. . .

The expressions, antagonist, antagonist to Dkk-1,
and the like within the scope of the present
invention are meant to include any molecule that interacts with
Dkk-1 and interferes with its function or
blocks or neutralizes a relevant activity of Dkk- 1,
by whatever means, depending on the indication being
treated. It may prevent the interaction between Dkk-1
and one or more of its receptors. Such agents
accomplish this effect in various ways. For instance, the class of
antagonists that neutralize a Dkk-1
activity will bind to Dkk- I with sufficient affinity and specificity to
interefere with Dkk- I as defined below.

An antibody that binds Dkk- 1 is one capable of
bindin cr that antigen with sufficient affinity such that the
antibody is useful as a therapeutic agent. . . the Dkk
Included within this group of antagonists are, for example, antibodies
directed against Dkk- I or
portions thereof reactive with Dkk-1, the Dkk- I
receptor or portions thereof reactive with Dkk-I, or any other
licrand that binds to Dkk The term also. . .
. . .
neutralize the activity of are used herein to mean, for example, block,
prevent, reduce, counteract the activity of, or make the Dkk-
1 ineffective by any mechanism. Therefore, the
antagonist may prevent a binding event necessary for activation of Dkk
By neutralizing antibody is
meant an antibody molecule as herein defined that is able to block or
significantly reduce an effector function
of the Dkk- 1. For example, a neutralizing antibody
may inhibit or reduce the ability of Dkk- I to interact with
a Dkk- I receptor. Alternatively, the neutralizing antibody may inhibit
or reduce the ability of Dkk- 1 to block
the Dkk- I receptor signalling pathway. The neutralizing antibody may
also immunospecifically bind to the
Dkk-1 in an immunoassay for Dkk-I activity such as
the ones described herein. It is a characteristic of the
neutralizing antibody of. . .

The term non-human transgenic animal that overexpresses dkk-
1 nucleic acid herein refers to a
non-human animal, such as a rodent, that has included within a plurality
of its cells. . .

The term non-human binary transgenic animal that expresses dkk
-1 nucleic acid herein refers to a
non-human animal, such as a rodent, in which gene expression is
controlled by the interaction of Dkk-1 on a
16
target transgene. These interactions are controlled by crossing animal
lines (such as rodent, e.g., mouse lines)
or by adding or. . .
. . .
diagnosing and treating insulin resistance and hypoinsulinemia
based on antagonists that bind to, and preferably neutralize, the
activity of Dkk
Further, Dkk- 1 itself is a useful treatment for
obesity and hyperinsulinemia.

Additionally, antagonists to Dkk-1 are further

indicated in methods herein for muscle repair and regeneration.

. . .

will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp. . .

. . .

in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin,. . .

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to. . .

Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC- I I mouse tumors available from the Salk Institute Cell Distribution Center,. . .

. . .

which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles. . .

Amino acid sequence modification(s) of the anti-Dkk-1 antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the. . . Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the anti-Dkk-1 antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses. . .

. . .

or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an anti-Dkk-1 antibody with an N-terminal methionyl residue or the antibody fused to a hypoglycemic polypeptide. Other insertional variants of the anti-Dkk- I antibody. . .

. . .

preparation by oligonucleotide-mediated (or site-directed) mutacrenesis, PCR niutagenesis, or cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-Dkk- 1 antibody.

. . .

serum half-life of the therapeutic antagonist. For example, a soluble immunoglobulin chimera,

such as described herein, can be
obtained for each specific Dkk-1 antagonist or
antagonistic portion thereof, as described in U.S. Pat. No.
. . .
The preferred dose is about 0 50 mg/kg/day, more
preferably about 0. I to 25 mg/kg/day. More preferred still, when the
Dkk- 1 antagonist is administered daily,
the intravenous or intramuscular dose for a human is about 0.3 to 10
mg/kg of body weight. . .
. . .
Preferred continuous dosing
schedules include daily continuous infusion, where Dkk- I antagonist is
infused each day, and continuous
bolus administration schedules, where Dkk-1
antagonist is administered at least once per day by bolus
injection or inhalant or intranasal routes. The invention also
encompasses discontinuous. . .
. . .
will vary according to the formulation,
method of delivery, and clinical needs of the mammal being treated. For
example, if the Dkk- 1 antagonist is
administered by infusion, administration schedules may comprise a first
period of administration followed by
a second period in which Dkk-. . .
. . .
the administration is by bolus injection, especially bolus injection of
a slow-release
formulation, dosing schedules may also be continuous in that Dkk
-1 antagonist is administered each day, or
may be discontinuous, with first and second periods as described above.
. . .
dosing schedule, and route of administration for the treatment of the
insulin-resistant or
hypoinsulinemic disorder or muscle condition. The containers of
Dkk-1 antagonist may be unit doses, bulk
packages (e.g., multi-dose packages), or sub-unit doses.
. . .
resilient stopper. Ampoules with non-
resilient, removable closures (e.g., sealed glass) or resilient stoppers
are most conveniently used for injectable
forms of Dkk-1 antagonist. Also contemplated are
packages for use in combination with a specific device,
such as an inhaler, a nasal administration device. . .

One specifically preferred method for administration of Dkk-
1 is by subcutaneous infusion,
particularly using a metered infusion device, such as a pump. Such pump
can be reusable or disposable,. . .

Therapeutic formulations of Dkk-1 suitable for
storage include mixtures of the Dkk-1 having the
desired degree of purity with pharmaceutically acceptable carriers,
excipients, or stabilizers (Remington's
Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)),. . . are
described in WO 97/04801. These compositions
comprise Dkk- I containing from about 0.1 to 90% by weight of the active
Dkk-1, preferably in a soluble
form, and more generally from about 10 to 30%.
. . .
methods. In
addition, sustained-release preparations may be prepared. Suitable
examples of sustained-release
preparations include semipermeable matrices of solid hydrophobic
polymers containing the Dkk-1, which

matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example,. . .

The Dkk-1 can bejoined to a carrier protein or PEG or POG or other molecule of this nature to increase its serum half-life,. . .

For treatment of hyperinsulinemia, the administration of Dkk-1 may occur in conjunction with, for example, diazoxide (see, for example, Shaer, Nephron, 89: 337-339 (2001)).

For treatment of obesity, the administration of Dkk-1 may occur without, or may be imposed with, a dietary restriction such as a limit in daily food or calorie intake, as is desired for the individual patient. In addition, the Dkk-1 is appropriately administered in combination with other treatments for combatting or preventing obesity, known herein as weight-loss agents. Substances useful for. . .

. . .

These weight-loss adjunctive agents and diazoxide may be administered at the same time as, before, or after the administration of the Dkk-1 and can be administered by the same or a different administration route than the Dkk- I is administered.

The dosages of Dkk-1 administered to an obese or hyperinsulinemic mammal will be determined by the physician in the light of the relevant circumstances, including the condition of the mammal, the type of Dkk-1, and the chosen route of administration. The dosage is preferably at a sufficiently low level as not to cause insulin-resistance, and. . . The preferred dose is about 0 50 32 mg/kg/day, more preferably about 0. I to 25 mg/kg/day. More preferred still, when the Dkk- 1 is administered daily, the intravenous or intramuscular dose for a human is about 0.3 to 10 mc,,r/kg of body weight per. . .

. . .

Dkk-I is administered by infusion, administration schedules may comprise a first period of administration followed by a second period in which Dkk-1 is not administered that is greater than, equal to, or less than the first period.

. . .

also provides kits for the treatment of obesity or hyperinsulinemia. The kits of the invention comprise one or more containers of Dkk- 1, preferably human Dkk- 1, in combination with a set of instructions, generally written instructions, relating to the use and dosage of Dkk- I for the. . .

Dkk- I may be packaged in any convenient, appropriate packaging. For example, if the Dkk- 1 is a freeze-dried formulation, an ampoule with a resilient stopper is normally used, so that the drug may be easily reconstituted by. . .

In one embodiment, one or more of the anti-Dkk-1 antibodies used in the assay is labeled; in another embodiment, a first is unlabeled, and a labeled, second antibody is used. . .

. . .
I antibody need not be labeled, and the
presence thereof can be detected using a labeled antibody which binds to
the Dkk-1 antibody.

In the assays of the present invention, an antigen such as Dkk
-1, or an antibody is preferably bound
to a solid phase support or carrier. By solid phase support or carrier
is intended. . .
. . .
a solid
phase matrix, preferably a microplate. The sample is brought in contact
with the Ab I -coated matrix such that
any Dkk-1 in the sample to which AM is specific
binds to the solid-phase Abl. Unbound sample components
are removed by washing. An. . .
. . .
the diagnostic assay. For instance, such
a kit can comprise an antibody or antibodies, preferably a pair of
antibodies to the Dkk- 1 anti cren that
preferably do not compete for the same binding site on the antigen. In a
specific embodiment, Dkk-1 may be
pre-adsorbed to the solid phase matrix. The kit preferably contains the
other necessary washing reagents well-
known in the art.. . . the art, and some are
exemplified below. The kit can optionally also comprise a Dkk-I
standard; ie., an amount of purified Dkk- 1
corresponding to a normal amount of Dkk- I in a standard sample.

In one aspect, a kit comprises in more than one container: an antibody
that binds Dkk-1, which can
be coated on a solid-phase carrier, e.g., a microtiter plate, a standard
sample containing Dkk-1, and
instructions for use in detection, wherein the antibody that binds Dkk-
I is detectably labeled or the kit further
comprises an. . .
. . .
cDNA such as inurine cDNA encoding Dkk- I or an appropriate sequence
thereof can
be used to clone genomic DNA encoding Dkk-1 in
accordance with established techniques, and the genomic
sequences are used to generate trans crenic animals that contain cells
that express DNA encoding Dkk- 1.
. . .
transgene incorporation with tissue-specific enhancers, which
results in targeted overexpression of Dkk Transgenic animals that
include a copy of a transgene encoding
Dkk-1 introduced into the crerm line of the animal
at an embryonic stage can be used to examine the effect of
increased. . .
. . .
a probe that is complementary to at least a portion of the transgene.
Western blot analysis
using an antibody against the Dkk-1 encoded by the
transcrene may be employed as an alternative or
additional method for screenina for the presence of the transcrene. .
.
. . .
specific type of cell. The most preferred such control element herein is
a muscle-
specific promoter that enables overexpression of the dkk-
1 nucleic acid (e.g., cDNA) in muscle tissue. An
example of such promoter is that described in Example I below or that.
. .

In another facet, non-human binary transgenic animals having altered dkk-1 nucleic acid expression
can be used to screen candidate drugs as set forth above, such as for their ability to reduce. . .

Example 1
Effects of Dkk-1 itz vivo and in vitro
Materials and Methods
L6 Cell culture
L6 myoblasts were proliferated in growth medium, composed of MEM alpha (Gibco-BRL). . . differentiation medium at
confluence (MEM alpha with 2% fetal calf serum). Cells were grown in this medium for 3-9 days and for
Dkk-1 treatments longer than 28 hours, dkk--1
(Krupnik et al., supra; WO 99/46281; DNA encoding
PRO1008) was added to this medium. Treatments. . .

Expression of Recombinant Dkk-I
The human homolog of Dkk-1 (hDkk-1) was expressed as
a C-terminal 8X His tag fusion (see
Krupnik et al., supra; and WO 99/46281, where PRO1008 is Dkk-1) in baculovirus and purified by nickel
affinity column chromatography. The identity of purified protein was verified by N-terminal sequence
analysis. The purified. . .

Glycogen Synthesi
Glycogen synthesis was determined as [14 Clglucose incorporation into glycooren. Control L6 cells
and cells treated with dkk-1 were incubated for 2
hours in serum-free MEM alpha containing [U-14 Q glucose
(5 mM crlucose; 1.25 pCi/n-d) with or without. . .
. . .
Chem., 253: 7570-7578 (1978)). Differentiated cells were treated with Dkk-I at 72 hours after the induction
of differentiation. For effect of Dkk-1 on 3T3L1
cell differentiation, Dkk-I was added to the medium at a
concentration of 40 nM during the initiation of differentiation. . .
. . .
3' to the pRK splice donor/acceptor site
that was preceded by the myosin light-chain promoter (Shani, Nature, 314: 283-286 (1985)). The dkk-1
cDNA was followed by the splice donor/acceptor sites present between the fourth and fifth exons of the
human growth hormone gene (Stewart. . .

When expressed in baculovirus, the human Dkk-1
protein was clipped internally to give a 16-kDa
cleavage product. In the gel shown in Fig. 2, band (a) corresponds to.
. .

The Dkk-1 effects of glucose uptake are independent
of the differentiation state of the cells and can
be seen even in cells that. . . uptake are dose-dependent. Fig. 4B shows that the decrease in basal and insulin-dependent glucose
uptake is seen upon 48-hour treatment with Dkk-1 at
concentrations as low as 10 nM.
. . .
regulated the expression of genes in the insulin
signaling pathway in L6 muscle cells. In particular, as shown in Fig. 7, Dkk-1 treatment increased the
expression of the p85 subunit of phosphoinositide 3-kinase significantly

(8.3 fold) following 48-hour
treatment, but did not significantly affect. . .
. . .
Dkk- I in mice resulted in impaired glucose tolerance and
reduced insulin production. Specifically, to confirm the in vivo effects
of Dkk-1 seen in transgenic mice,
female FVB mice were injected intravenously with Dkk-1 for 8 days
(single daily injection of 0.05 and 0.2
mg/kg/day). The effects of Dkk- 1 on glucose
tolerance were measured 48 hours and 8 days after the start of
injection. Glucose tolerance was unaffected with 48. . .

Overexpression of Dkk-1 in mice affected growth, body composition, and
metabolism. Particularly,
Transcrenic FVB mice overexpressing the dkk-1
transgene under control of the MLC promoter were
generated (Shani, supra). Body weights of control and transgenic animals
were followed over. . .

45
Table 2
Control Control Dkk-I Dkk-1
Regular diet Regular diet transgenic transgenic
Physiological Parameter (males, n=8) (females, n=4) Regular diet Regular
diet
males, n=4) (females, n=8)
Body Weight at 16. . . ,
. . .
signaling inhibits adipogenesis. To determine whether Dkk-I affected
body composition, some
animals were placed on a high-fat diet for 24 weeks. Dkk-
1 transgenic animals on a high-fat diet also showed
significantly reduced body weights than their wild-type littermates
(Fig. 15A), with comparable reduction. . .

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Table 3
Control Control Dkk-1 TG Dkk-1
TG
High-fat diet High-fat diet High-fat diet High-fat diet
eter (m--12) (f=8) m=6) (f=5)
Body Weight at 16 of
40.3 ± 6.6 34.7 ±. . .
. . .
diabetes, can be affected by expression levels, phosphorylation, and
activity of
proteins in the insulin- signaling pathway. Therefore, the effects of
Dkk-1 in muscle both in vivo and in vitro
were investigated.
. . .
animals also had reduced levels of serum insulin, although no effects
were seen in the serum insulin levels in transgenic mice. Dkk-
1 reduced the basal and insulin-stimulated
glucose uptake in L6 cells through inhibition of Akt, a key intermediate
in the insulin-signaling pathway.

These effects of Dkk-1 were seen only after 18 hrs
of exposure to Dkk-1.
. . .
size with a proportional decrease in the
weight of various organs. Without beinor limited to any one theory,
these effects of Dkk-1 are likely to be
mediated through the reduction in insulin (and likely IGF-1)-stimulated
Akt activity. Direct evidence for this

comes from studies. . .

Chem., 276: 19664-19671 (2001)). Alternatively, without limitation to any one theory, the reduced growth
rate in dkk-1 transgenic animals could be a
secondary effect of the reduced glucose uptake and consequent
alteration in nutrient availability and metabolic rate. . .

Primary 3T3LI preadipocytes were stimulated to differentiate in the presence or absence of Dkk-1,
cells were collected at different days after the start of
differentiation, and the transcripts analysed for
expression levels of markers of adipocyte differentiation such as AP2, PPARy, CEB P(x, and FAS. Dkk- 1
treatment did not alter levels of FAS and AP2; however, PPARylevels were about 2-fold reduced in Dkk-1-
treated cells and C/EBPoc levels. . .

. . .

adipose tissue mass and are up-regulated by
Akt (Barthel et al., Endocrinolo -3562 (1997)). The reduced levels of circulating leptin in dkk-1
138: 3559
48
transgenic animals could be a direct effect of decreased adipose mass and/or decreased Akt activity in
adipose tissue, without being limited. . .

A significant reduction in the levels of secreted insulin was observed herein following 8 days of
Dkk-1 injection, and smaller effects in transgenic
animals overexpressing dkk-1 in the muscle. Without
being
limited to any one theory, the stronger effects in injected animals could be a result of. . . there may be smaller differences
in insulin levels either due to compensatory mechanisms or due to a more localized effect of Dkk-1 in the
muscle. Since Akt is known to stimulate islet cell proliferation and insulin production, and since the data
herein show for the first time that Dkk-1-injected and transgenic mice have lower insulin levels, an antagonist
to Dkk- 1 is now found useful in treating
hypoinsulinemia, and conversely, Dkk- I itself is found useful in treating hyperinsulinemia.

. . .

in L6 muscle cells as well as in transgenic mice overexpressin cr
the protein in muscle. Treatment of muscle cells with Dkk-
1 resulted in a decrease in the basal and insulin-
stimulated glucose uptake. This effect was observed following both short-term and long-term treatment,
49
suggesting, without being limited to any one theory, that Dkk-
1 may affect both the activity as well as the
expression levels of proteins in the insulin signaling pathway. Consistent with this. . .

. . .

obesity and hyperinsulinernia, as well as being useful as a diagnostic marker in assays for such conditions. Also, an antagonist to Dkk-1 is expected to inhibit the
progression of the diabetes phenotype in transgenic animal models disclosed in U.S. Pat. No. 6,187,991.

Example 2
Development of Anti-Dkk-1 Monoclonal Antibodies
Five female Balb/c mice (Charles River Laboratories, Wilmington, DE)

were hyperimmunized with
purified recombinant polyhistidine-tagged (HIS8) human Dkk- I expressed.
. . used for each animal, administered via footpad. After five
injections,
B-cells from the lymph nodes of the five mice, demonstrating high anti-
Dkk- 1 antibody titers, were fused
with mouse myeloma cells (X63.Ag8.653; American Type Culture
Collection, Manassas, VA) using the
protocols described in Kohler and Milstein, supra, and Hongo et al.,. .
.

All the seven antibody preparations bound Dkk-1 in
Western immunoblots.

L6 cells were differentiated and treated for 48 hours in the absence of
Dkk-1 (control) or in the
presence of 40 nM Dkk-1 (plus or minus anti-
Dkk-1 antibody 1G1.2D12.2D1 1 (ATCC No. PTA-3086) in
an
amount of 0.5 ttg/mL). Basal and insulin-stimulated glucose uptake in
the L6 cells. . .

50
Designation ATQC Dep. No. Deposit Date
DKKI.MAB3139,8CI 1.2GI 1. IDI PTA-3084 February 21, 2001
DKK1.MAB3143.4C7.2HI0.2GI PTA-3085 February 21, 2001
DKKLMAB3142. I G1.21) 12.2131 1 PTA-3086 February 21, 2001
DKK1.MAB3141.5B12.2C5.2A5 PTA-3087 February 21, 2001
DKKLMAB313 8.7C 1 1 16.2AS PTA-3088 February 21, 2001
DKK1.MAB3140.7B2.2A6.2H4 PTA-3089 February 21, 2001
DKK1.MAB3144.5A2.2A8.1C3 PTA-3097 February 21, 2001
This deposit was made under the provisions of the Budapest Treaty on the
International Recognition
of the Deposit. . .

CLMEN. . . insulin resistance or hypoinsulinemia in marnmals comprising
administering to a
mammal in need thereof an effective amount of an antagonist to
Dickkopf- 1 (Dkk- 1).

4 The method of claim 1 wherein the antacronist is an antibody that
binds Dkk- 1.
5 . The method of claim 4 wherein the antibody is a monoclonal antibody.
. . .
presence or onset of insulin resistance or hypoinsulinernia in a mammal
comprising the steps of:
(a) measuring the amount of Dickkopf- I (Dkk- 1) in
a sample from said mammal; and
(b) comparing the amount determined in step (a) to an amount of Dkk- I.
. .

12 The method of claim I I wherein the anti-Dkk- 1
antibody comprises a label.

16 The method of claim IO wherein the mammal is human and human
Dkk- 1 is being measured.

17 A kit for treating insulin resistance or hypoinsulinemia, said kit
comprising:
(a) a container comprising an antagonist to Dkk-1;
and
(b) instructions for using the antagonist to treat insulin resistance or
hypoinsulinernia.

18 The kit of claim 17 wherein the antagonist is an antibody that binds Dkk- 1

20 The kit of claim 18 wherein the antibody binds human Dkk-1.

26 A method of treating obesity or hyperinsulinemia in mammals comprising administering to a mammal in need thereof an effective amount of Dickkopf-I (Dkk-1).

. . .

for detecting the presence or onset of obesity or hyperinsulinemia in a mammal comprising the steps of.
(a) measuring the amount of Dickkopf-1 (Dkk]l) in a sample from said mammal; and
(b) comparing the amount determined in step (a) to an amount of Dkk-l present in a standard sample, a decreased level in the amount of Dkk-1 in step (a) being indicative of obesity or hyperinsulinemia.

36 A kit for treating obesity or hyperinsulinemia, said kit comprising:
(a) a container comprising Dkk- 1; and
(b) instructions for using the Dkk- I to treat obesity or hyperinsulinemia.

. . .

the presence or onset of insulin resistance, hyperinsulinemia, hypoinsulinemia, or obesity, said kit comprising:
(a) a container comprising an antibody that binds Dickkopf-1 (Dkk-1);
(b) a container comprising a standard sample containing Dkk-1; and
(c) instructions for using the antibody and standard sample to detect insulin resistance, hyperinsulinemia, hypoinsulinemia, or obesity, wherein either the antibody. . .

41 The kit of claim 39 wherein the Dkk-l is human Dkk-1 and the kit is for detecting non-insulin dependent diabetes or obesity.
53
. A method for repairing or regeneratingmusele in a mammal comprising.
. .

47 A monoclonal antibody preparation prepared by hyperimmunizing mice with tagged Dkk-1 diluted in an adjuvant, fusing B-cells from the mice having anti-Dkk-I antibody titers with mouse myeloma cells and obtaining supernatants, harvesting the supernatants, screening the harvested supernatants for antibody production, injecting positive clones showing the highest immunobinding after. . .

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

L1	3942	S WNT
L2	244	S L1 (S) ANTAGON?
L3	553450	S OSTEO? OR BONE
L4	70	S L3 AND L2
L5	22597	S MULTIPLE MYELOMA

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L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11
L15           19 S L13 AND L3
L16           14 S L15 AND EXPRESS?
L17            6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18         4365 S WNT
L19          273 S L1 (S) ANTAGON?
L20          273 S L18 (S) ANTAGON?
L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29         1307 S WNT
L30          161 S L29 (S) ANTAG?
L31           46 S (DICKKOPF () 1) OR (DKK () 1)
L32           62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33           62 S L32 OR L31
L34        27031 S OSTEO?
L35        59451 S L34 OR BONE
L36        87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37        14570 S MYELOMA
L38           39 S L33 AND L34
L39           18 S L38 AND L37
L40            8 S L39 NOT PY>2002
L41           10 S L33/CLM
L42            1 S L41 AND L40
L43            4 S L33/AB
L44            1 S L42 AND L35

=> s d ibib
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             18 IBIB
L45           0 D IBIB
                 (D(W)IBIB)

=> d l44 ibib

L44    ANSWER 1 OF 1      PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2002066509 PCTFULL  ED 20020910  EW 200235
TITLE (ENGLISH):         TREATMENT INVOLVING DKK-1 OR
                         ANTAGONISTS THEREOF
TITLE (FRENCH):          TRAITEMENT FAISANT APPEL A DKK-1 OU
                         AUX ANTAGONISTES DE DKK-1
INVENTOR(S):             DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
                         San Mateo, CA 94403, US;
                         STEWART, Timothy A., 465 Douglas Street, San Francisco,
                         CA 94114, US
PATENT ASSIGNEE(S):      GENENTECH, INC., 1 DNA Way, South San Francisco, CA
                         94080, US [US, US]
```

AGENT: HASAK, Janet E.$, GENENTECH, INC., MS 49, 1 DNA Way, South San Francisco, CA 94080-4990$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002066509	A2	20020829

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-US4573 A 20020215
PRIORITY INFO.: US 2001-60/269,435 20010216

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                                                 ENTRY    SESSION
FULL ESTIMATED COST                              16.18      62.30

FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
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FILE COVERS 1861 TO 28 JUN 2005 (20050628/ED)
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             1 DICKKOPFS
             3 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
        354082 1
             2 DICKKOPF-1
                 (DICKKOPF(W)1)
             2 DKK1
             3 DKK
             1 DKKS
             3 DKK
                 (DKK OR DKKS)
        354082 1
             2 DKK-1
                 (DKK(W)1)
L46          4 DICKKOPF-1 OR DKK1 OR DKK-1

=> s osteo?
L47       3245 OSTEO?
```

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=> s l47 and l46
L48           0 L47 AND L46

=> s l46 and myeloma
            547 MYELOMA
             32 MYELOMAS
            567 MYELOMA
                  (MYELOMA OR MYELOMAS)
L49           0 L46 AND MYELOMA

=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1          3942 S WNT
L2           244 S L1 (S) ANTAGON?
L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11
L15           19 S L13 AND L3
L16           14 S L15 AND EXPRESS?
L17            6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18         4365 S WNT
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L20          273 S L18 (S) ANTAGON?
L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29         1307 S WNT
L30          161 S L29 (S) ANTAG?
L31           46 S (DICKKOPF () 1) OR (DKK () 1)
L32           62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33           62 S L32 OR L31
L34        27031 S OSTEO?
L35        59451 S L34 OR BONE
L36        87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37        14570 S MYELOMA
L38           39 S L33 AND L34
L39           18 S L38 AND L37
L40            8 S L39 NOT PY>2002
L41           10 S L33/CLM
L42            1 S L41 AND L40
L43            4 S L33/AB
L44            1 S L42 AND L35
L45            0 S D IBIB
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     FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
L46            4 S DICKKOPF-1 OR DKK1 OR DKK-1
L47         3245 S OSTEO?
L48            0 S L47 AND L46
L49            0 S L46 AND MYELOMA

=> file pctfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.82      63.12

FILE 'PCTFULL' ENTERED AT 13:17:23 ON 25 JUL 2005
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FILE LAST UPDATED:          19 JUL 2005      <20050719/UP>
MOST RECENT UPDATE WEEK:        200528        <200528/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s l43 and l35
L50            4 L43 AND L35

=> d ibib 1-4

L50    ANSWER 1 OF 4      PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2005049640 PCTFULL  ED 20050607  EW 200522
TITLE (ENGLISH):         RHESUS MONKEY DICKKOPF-1, NUCLEOTIDES ENCODING SAME,
                         AND USES THEREOF
TITLE (FRENCH):          PROTEINE DICKKOPF-1 DE SINGE RHESUS, NUCLEOTIDES CODANT
                         LADITE PROTEINE, ET PROCEDES D'UTILISATION
INVENTOR(S):             HARADA, Shun-ichi, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [JP, US];
                         KASPARCOVA, Viera, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [CZ, US];
                         GLANTSCHNIG, Helmut, 126 East Lincoln Avenue, Rahway,
                         NJ 07065-0907, US [AT, US]
PATENT ASSIGNEE(S):      MERCK & CO., INC., 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [US, US], for all designates States
                         except US;
                         HARADA, Shun-ichi, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [JP, US], for US only;
                         KASPARCOVA, Viera, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [CZ, US], for US only;
                         GLANTSCHNIG, Helmut, 126 East Lincoln Avenue, Rahway,
                         NJ 07065-0907, US [AT, US], for US only
AGENT:                   MERCK & CO., INC.$, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907$, US
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2005049640        A2 20050602
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO
                         CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR
                         HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
                         MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO
                         RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LU MC NL PL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2004-US38489 A 20041112
PRIORITY INFO.: US 2003-60/520,708 20031117

L50 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2004053063 PCTFULL ED 20040630 EW 200426
TITLE (ENGLISH): MOLECULAR DETERMINANTS OF MYELOMA BONE DISEASE AND USES THEREOF
TITLE (FRENCH): DETERMINANTS MOLECULAIRES DE MALADIE OSSEUSE DE TYPE MYELOME ET UTILISATIONS DE CEUX-CI
INVENTOR(S): SHAUGHNESSY, John, D., 4317 Old Oak Drive, Little Rock, AR 72222, US
PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ARKANSAS, 2404 North University Avenue, Little Rock, AR 72207-3608, US [US, US]
AGENT: ADLER, Benjamin, A.$, Adler & Associates, 8011 Candle Lane, Houston, TX 77071$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004053063	A2	20040624

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
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RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-US38372 A 20031204
PRIORITY INFO.: US 2002-60/431,040 20021205

L50 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002092015 PCTFULL ED 20021210 EW 200247
TITLE (ENGLISH): REAGENTS AND METHODS FOR MODULATING DKK-MEDIATED INTERACTIONS
TITLE (FRENCH): REACTIFS ET PROCEDES DESTINES A MODULER DES INTERACTIONS INDUITES PAR DKK
INVENTOR(S): ALLEN, Kristina, 11 Oliver Lane, Hopkinton, MA 01748-3108, US [US, US];
ANISOWICZ, Anthony, 50 Upham Street, West Newton, MA 02465, US [US, US];
BHAT, Bheem, M., 1214 Mayapple Lane, West Chester, PA 19380, US [IN, US];
DAMAGNEZ, Veronique, 125 Water Street, Framingham, MA 01701, US [FR, US];
ROBINSON, John, Allen, 23 Webb Road, Downingtown, PA 19335, US [US, US];
YAWORSKY, Paul, J., 13 Hobart Lane, Rockland, MA 02370, US [US, US]
PATENT ASSIGNEE(S): GENOME THERAPEUTICS CORPORATION, 100 Beaver Street, Waltham, MA 02453, US [US, US], for all designates States except US;
WYETH, Five Giralda Farms, Madison, NJ 07928, US [US, US], for all designates States except US;
ALLEN, Kristina, 11 Oliver Lane, Hopkinton, MA

01748-3108, US [US, US], for US only;
ANISOWICZ, Anthony, 50 Upham Street, West Newton, MA 02465, US [US, US], for US only;
BHAT, Bheem, M., 1214 Mayapple Lane, West Chester, PA 19380, US [IN, US], for US only;
DAMAGNEZ, Veronique, 125 Water Street, Framingham, MA 01701, US [FR, US], for US only;
ROBINSON, John, Allen, 23 Webb Road, Downingtown, PA 19335, US [US, US], for US only;
YAWORSKY, Paul, J., 13 Hobart Lane, Rockland, MA 02370, US [US, US], for US only

AGENT: REA, Teresa, Stanek$, Burns, Doane, Swecker & Mathis L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002092015	A2	20021121

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
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RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-US15982 A 20020517
PRIORITY INFO.: US 2001-60/291,311 20010517
US 2002-60/353,058 20020201
US 2002-60/361,293 20020304

L50 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002066509 PCTFULL ED 20020910 EW 200235
TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES DE DKK-1

INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116, San Mateo, CA 94403, US;
STEWART, Timothy A., 465 Douglas Street, San Francisco, CA 94114, US

PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA 94080, US [US, US]

AGENT: HASAK, Janet E.$, GENENTECH, INC., MS 49, 1 DNA Way, South San Francisco, CA 94080-4990$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002066509	A2	20020829

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

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APPLICATION INFO.:       WO 2002-US4573       A  20020215
PRIORITY INFO.:          US 2001-60/269,435       20010216


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     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1          3942 S WNT
L2           244 S L1 (S) ANTAGON?
L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
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L15           19 S L13 AND L3
L16           14 S L15 AND EXPRESS?
L17            6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
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L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
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L44            1 S L42 AND L35
L45            0 S D IBIB

     FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
L46            4 S DICKKOPF-1 OR DKK1 OR DKK-1
```

```
L47         3245 S OSTEO?
L48            0 S L47 AND L46
L49            0 S L46 AND MYELOMA

     FILE 'PCTFULL' ENTERED AT 13:17:23 ON 25 JUL 2005
L50            4 S L43 AND L35

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     5.34      68.46

STN INTERNATIONAL LOGOFF AT 13:18:35 ON 25 JUL 2005


Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  FEB 28  PATDPAFULL - New display fields provide for legal status
                  data from INPADOC
 NEWS  4  FEB 28  BABS - Current-awareness alerts (SDIs) available
 NEWS  5  MAR 02  GBFULL: New full-text patent database on STN
 NEWS  6  MAR 03  REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 22  KOREAPAT now updated monthly; patent information enhanced
 NEWS  9  MAR 22  Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  10 MAR 22  PATDPASPC - New patent database available
 NEWS  11 MAR 22  REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS  12 APR 04  EPFULL enhanced with additional patent information and new
                  fields
 NEWS  13 APR 04  EMBASE - Database reloaded and enhanced
 NEWS  14 APR 18  New CAS Information Use Policies available online
 NEWS  15 APR 25  Patent searching, including current-awareness alerts (SDIs),
                  based on application date in CA/CAplus and USPATFULL/USPAT2
                  may be affected by a change in filing date for U.S.
                  applications.
 NEWS  16 APR 28  Improved searching of U.S. Patent Classifications for
                  U.S. patent records in CA/CAplus
```

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 NEWS  17 MAY 23  GBFULL enhanced with patent drawing images
 NEWS  18 MAY 23  REGISTRY has been enhanced with source information from
                  CHEMCATS
 NEWS  19 JUN 06  The Analysis Edition of STN Express with Discover!
                  (Version 8.0 for Windows) now available
 NEWS  20 JUN 13  RUSSIAPAT: New full-text patent database on STN
 NEWS  21 JUN 13  FRFULL enhanced with patent drawing images
 NEWS  22 JUN 27  MARPAT displays enhanced with expanded G-group definitions
                  and text labels
 NEWS  23 JUL 01  MEDICONF removed from STN
 NEWS  24 JUL 07  STN Patent Forums to be held in July 2005
 NEWS  25 JUL 13  SCISEARCH reloaded
 NEWS  26 JUL 20  Powerful new interactive analysis and visualization software,
                  STN AnaVist, now available

 NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *


*ENCOMPPAT    - EnCompass Patent File 1964-present (Supporters)
*ENCOMPPAT2   - EnCompass Patent File 1964-Present (Non-Supporters)

  * The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005

 FILE LAST UPDATED: 23 JUL 2005 (20050723/UP).  FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available.  For details enter HELP
 RLOAD at an arrow promt (=>).  See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
```

```
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s bone
        424243 BONE
         91740 BONES
L1      446342 BONE
                 (BONE OR BONES)

=> s (dickkopf () 1) or (dickkopf-1) or dickkopf1 or (dkk1) or (dkk-1) or (dkk () 1)
            85 DICKKOPF
             8 DICKKOPFS
            90 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
       3513889 1
            49 DICKKOPF (W) 1
            85 DICKKOPF
             8 DICKKOPFS
            90 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
       3513889 1
            49 DICKKOPF-1
                 (DICKKOPF(W)1)
            17 DICKKOPF1
           106 DKK1
           119 DKK
             9 DKKS
           121 DKK
                 (DKK OR DKKS)
       3513889 1
            44 DKK-1
                 (DKK(W)1)
           119 DKK
             9 DKKS
           121 DKK
                 (DKK OR DKKS)
       3513889 1
            44 DKK (W) 1
L2         133 (DICKKOPF (W) 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DKK-
               1) OR (DKK (W) 1)

=> s l2 and l1
L3          36 L2 AND L1

=> s l3 not py>2002
      1489868 PY>2002
L4          12 L3 NOT PY>2002

=> s l4 and express?
        932565 EXPRESS?
L5            9 L4 AND EXPRESS?

=> d ibib 1-4

L5   ANSWER 1 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2002693855     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12455632
TITLE:              Bmp, Fgf and Wnt signalling in programmed cell death and
                    chondrogenesis during vertebrate limb development: the role
                    of Dickkopf-1.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Institut fur Entwicklungs- und Molekularbiologie der Tiere
```

(EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SOURCE: International journal of developmental biology, (2002) 46 (7) 943-7.
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030619
Entered Medline: 20030618

L5 ANSWER 2 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2002131765 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11867524
TITLE: The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AUTHOR: Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE: Entwicklungs- und Molekularbiologie der Tiere, Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany.. lars.grotewold@uni-duesseldorf.de
SOURCE: EMBO journal, (2002 Mar 1) 21 (5) 966-75.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

L5 ANSWER 3 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001447406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291860
TITLE: The role of the homeodomain protein Bozozok in zebrafish axis formation.
AUTHOR: Solnica-Krezel L; Driever W
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SOURCE: International journal of developmental biology, (2001) 45 (1) 299-310.
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L5 ANSWER 4 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001447398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291852
TITLE: Dickkopf1 and the Spemann-Mangold head organizer.
AUTHOR: Niehrs C; Kazanskaya O; Wu W; Glinka A
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: International journal of developmental biology, (2001) 45 (1) 237-40. Ref: 34

Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

=> d ibib 5-7

L5 ANSWER 5 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001168646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11269304
TITLE: Development. The path to the heart and the road not taken.
AUTHOR: Olson E N
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.. eolson@hamon.swmed.edu
SOURCE: Science, (2001 Mar 23) 291 (5512) 2327-8.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20021218
Entered Medline: 20010412

L5 ANSWER 6 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

L5 ANSWER 7 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001069917 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11044411
TITLE: The role of Xenopus dickkopf1 in prechordal plate specification and neural patterning.
AUTHOR: Kazanskaya O; Glinka A; Niehrs C
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany.
SOURCE: Development (Cambridge, England), (2000 Nov) 127 (22) 4981-92.

Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010104

=> d his

(FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1 446342 S BONE
L2 133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3 36 S L2 AND L1
L4 12 S L3 NOT PY>2002
L5 9 S L4 AND EXPRESS?

=> d ibib 8-9

L5 ANSWER 8 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2000108581 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10640703
TITLE: Requirement for anti-dorsalizing morphogenetic protein in organizer patterning.
AUTHOR: Dosch R; Niehrs C
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (2000 Feb) 90 (2) 195-203.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000427

L5 ANSWER 9 OF 9 MEDLINE on STN
ACCESSION NUMBER: 1999425169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10495270
TITLE: Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AUTHOR: Monaghan A P; Kioschis P; Wu W; Zuniga A; Bock D; Poustka A; Delius H; Niehrs C
CORPORATE SOURCE: Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (1999 Sep) 87 (1-2) 45-56.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ243963; GENBANK-AJ243964
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327

Entered Medline: 20000316

=> d 1-4

L5 ANSWER 1 OF 9 MEDLINE on STN
AN 2002693855 MEDLINE
DN PubMed ID: 12455632
TI Bmp, Fgf and Wnt signalling in programmed cell death and chondrogenesis during vertebrate limb development: the role of Dickkopf-1.
AU Grotewold Lars; Ruther Ulrich
CS Institut fur Entwicklungs- und Molekularbiologie der Tiere (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SO International journal of developmental biology, (2002) 46 (7) 943-7. Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20021214
Last Updated on STN: 20030619
Entered Medline: 20030618

L5 ANSWER 2 OF 9 MEDLINE on STN
AN 2002131765 MEDLINE
DN PubMed ID: 11867524
TI The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AU Grotewold Lars; Ruther Ulrich
CS Entwicklungs- und Molekularbiologie der Tiere, Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany.. lars.grotewold@uni-duesseldorf.de
SO EMBO journal, (2002 Mar 1) 21 (5) 966-75. Journal code: 8208664. ISSN: 0261-4189.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

L5 ANSWER 3 OF 9 MEDLINE on STN
AN 2001447406 MEDLINE
DN PubMed ID: 11291860
TI The role of the homeodomain protein Bozozok in zebrafish axis formation.
AU Solnica-Krezel L; Driever W
CS Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SO International journal of developmental biology, (2001) 45 (1) 299-310. Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L5 ANSWER 4 OF 9 MEDLINE on STN
AN 2001447398 MEDLINE

DN PubMed ID: 11291852
TI Dickkopf1 and the Spemann-Mangold head organizer.
AU Niehrs C; Kazanskaya O; Wu W; Glinka A
CS Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SO International journal of developmental biology, (2001) 45 (1) 237-40.
Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

=> d kwic 4

L5 ANSWER 4 OF 9 MEDLINE on STN
TI Dickkopf1 and the Spemann-Mangold head organizer.
AB . . . the Spemann-Mangold organizer may be mediated by secreted Wnt antagonists. Wnts are potent posteriorizing factors and antagonize the Spemann-Mangold organizer. Dickkopf1 (dkk1) encodes a secreted effector expressed in head organizing centers of Xenopus, mouse and zebrafish. It acts as a Wnt inhibitor and is able together with. . . anteriorizes both mesendoderm and neuroectoderm, promoting prechordal plate and forebrain fates. Injection of inhibitory antibodies leads to microcephaly and cyclopia. Dkk1 thus is an essential mediator of the vertebrate head organizer.
CT Animals
Body Patterning
Bone Morphogenetic Proteins: AI, antagonists & inhibitors
Embryonic Induction
Head: EM, embryology
Mice
*Organizers, Embryonic: PH, physiology
Proteins: GE, genetics
. . .
CN 0 (Bone Morphogenetic Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1 protein, Xenopus); 0 (wnt8b protein, zebrafish)

=> d kwic 2

L5 ANSWER 2 OF 9 MEDLINE on STN
TI The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AB Dickkopf-1 (Dkk-1) has been shown to be a potent inhibitor of Wnt/beta-catenin signaling in a variety of assays and organisms. In this study, we show that expression of Dkk-1 overlaps significantly with the sites of programmed cell death in normal as well as mutant vertebrate limb development, and identify several of its upstream regulators, one of which is Bmp-4. Interestingly, Bmp-4 only activates Dkk-1 when it concomitantly induces apoptosis. Moreover, Dkk-1 is heavily up-regulated by UV irradiation and several other genotoxic stimuli. We further show that normal expression of Dkk-1 is dependent on the Ap-1 family member c-Jun and that overexpression of Dkk-1 enhances Bmp-triggered

```
     apoptosis in the vertebrate limb.  Taken together, our results provide
     evidence for an important role of Dkk-1-mediated
     inhibition of Wnt/beta-catenin signaling in response to different stress
     signals that all converge on the activation of c-Jun in vivo.
CT    Animals
      Apoptosis: GE, genetics
      Apoptosis: PH, physiology
        Bone Morphogenetic Proteins: AI, antagonists & inhibitors
        Bone Morphogenetic Proteins: PD, pharmacology
       *Bone Morphogenetic Proteins: PH, physiology
      Chick Embryo
      Cytoskeletal Proteins: AI, antagonists & inhibitors
      DNA-Binding Proteins: BI, biosynthesis
      DNA-Binding Proteins: GE, genetics
.  .  .  Implants
      Enzyme Inhibitors: PD, pharmacology
     *Extremities: EM, embryology
      Fibroblast Growth Factors: PD, pharmacology
      Fibroblasts: DE, drug effects
      Fibroblasts: ME, metabolism
        Gene Expression Regulation, Developmental: DE, drug effects
       *Gene Expression Regulation, Developmental: PH, physiology
        Gene Expression Regulation, Developmental: RE, radiation effects
      Mesoderm: ME, metabolism
      Mice
      Mice, Knockout
      Morphogenesis
      Protein Biosynthesis
      Proteins: GE, genetics
      Proteins:.  .  .
CN    0 (Bone Morphogenetic Proteins); 0 (Cytoskeletal Proteins); 0
     (DNA-Binding Proteins); 0 (Drug Implants); 0 (Enzyme Inhibitors); 0
     (Proteins); 0 (Proto-Oncogene Proteins); 0.  .  .  0 (Recombinant Fusion
     Proteins); 0 (Trans-Activators); 0 (Transcription Factor AP-1); 0
     (Transcription Factors); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (
     bone morphogenetic protein 4); 0 (dkk1 protein,
     Xenopus); 0 (hedgehog protein, vertebrate); 0 (lymphoid enhancer-binding
     factor 1); 0 (wnt8b protein, zebrafish)


=> d kwic 5

L5   ANSWER 5 OF 9     MEDLINE on STN
CT    Animals
     *Blood Cells
        Bone Morphogenetic Proteins: ME, metabolism
      Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
      Central Nervous System: EM, embryology
      Central Nervous System: ME, metabolism
      Cytoskeletal Proteins: ME, metabolism
      Drosophila: EM, embryology
      Drosophila: ME, metabolism
     *Drosophila Proteins
     *Embryonic Induction
      Endoderm: PH, physiology
        Gene Expression Regulation, Developmental
      Glycogen Synthase Kinase 3
     *Heart: EM, embryology
      Hematopoiesis
      Insect Proteins: ME, metabolism
      Mesoderm: CY, cytology
      Mesoderm:.  .  .
CN    0 (Bone Morphogenetic Proteins); 0 (Cytoskeletal Proteins); 0
     (Drosophila Proteins); 0 (Insect Proteins); 0 (Proteins); 0
```

(Trans-Activators); 0 (Transcription Factors); 0 (Wnt-3 protein); 0 (Xenopus Proteins); 0 (crescent protein, Xenopus); 0 (dkk1 protein, Xenopus); 0 (dpp protein, Drosophila); 0 (wnt8a protein, Zebrafish); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (Glycogen Synthase. . .

```
=> s osteo?
L6      211167 OSTEO?

=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1       446342 S BONE
L2          133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3           36 S L2 AND L1
L4           12 S L3 NOT PY>2002
L5            9 S L4 AND EXPRESS?
L6       211167 S OSTEO?

=> s l2 and l6
L7           24 L2 AND L6

=> s l5 not py>2002
       1489868 PY>2002
L8            9 L5 NOT PY>2002

=> s l8 not py>2001
       2029769 PY>2001
L9            7 L8 NOT PY>2001

=> d ibib 1-4

L9   ANSWER 1 OF 7     MEDLINE on STN
ACCESSION NUMBER:   2001447406     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11291860
TITLE:              The role of the homeodomain protein Bozozok in zebrafish
                    axis formation.
AUTHOR:             Solnica-Krezel L; Driever W
CORPORATE SOURCE:   Department of Molecular Biology, Vanderbilt University,
                    Nashville, Tennessee 37235, USA.. lilianna.solnica-
                    krezel@vanderbilt.edu
SOURCE:             International journal of developmental biology, (2001) 45
                    (1) 299-310.
                    Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY:       Spain
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200108
ENTRY DATE:         Entered STN: 20010813
                    Last Updated on STN: 20010813
                    Entered Medline: 20010809

L9   ANSWER 2 OF 7     MEDLINE on STN
ACCESSION NUMBER:   2001447398     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11291852
TITLE:              Dickkopf1 and the Spemann-Mangold head organizer.
AUTHOR:             Niehrs C; Kazanskaya O; Wu W; Glinka A
CORPORATE SOURCE:   Division of Molecular Embryology, Deutsches
                    Krebsforschungszentrum, Heidelberg, Germany.
SOURCE:             International journal of developmental biology, (2001) 45
```

(1) 237-40. Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L9 ANSWER 3 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001168646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11269304
TITLE: Development. The path to the heart and the road not taken.
AUTHOR: Olson E N
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA..
eolson@hamon.swmed.edu
SOURCE: Science, (2001 Mar 23) 291 (5512) 2327-8.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20021218
Entered Medline: 20010412

L9 ANSWER 4 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

=> d kwic 2

L9 ANSWER 2 OF 7 MEDLINE on STN
TI Dickkopf1 and the Spemann-Mangold head organizer.
AB . . . the Spemann-Mangold organizer may be mediated by secreted Wnt antagonists. Wnts are potent posteriorizing factors and antagonize the Spemann-Mangold organizer. Dickkopf1 (dkk1) encodes a secreted effector expressed in head organizing centers of Xenopus, mouse and zebrafish. It acts as a Wnt inhibitor and is able together with. . . anteriorizes both mesendoderm and neuroectoderm, promoting prechordal plate and forebrain fates. Injection of inhibitory antibodies leads to microcephaly and cyclopia. Dkk1 thus is an

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     essential mediator of the vertebrate head organizer.
CT    Animals
      Body Patterning
        Bone Morphogenetic Proteins: AI, antagonists & inhibitors
      Embryonic Induction
      Head: EM, embryology
      Mice
     *Organizers, Embryonic: PH, physiology
      Proteins: GE, genetics
.  .  .
CN   0 (Bone Morphogenetic Proteins); 0 (Proteins); 0 (Proto-Oncogene
     Proteins); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1
     protein, Xenopus); 0 (wnt8b protein, zebrafish)


=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1       446342 S BONE
L2          133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3           36 S L2 AND L1
L4           12 S L3 NOT PY>2002
L5            9 S L4 AND EXPRESS?
L6       211167 S OSTEO?
L7           24 S L2 AND L6
L8            9 S L5 NOT PY>2002
L9            7 S L8 NOT PY>2001

=> s l7 not py>2001
       2029769 PY>2001
L10           0 L7 NOT PY>2001

=> s l7 not py>2002
       1489868 PY>2002
L11           3 L7 NOT PY>2002

=> d ibib 1-3

L11  ANSWER 1 OF 3     MEDLINE on STN
ACCESSION NUMBER:   2002280313     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12021176
TITLE:              Global gene profiling in human endometrium during the
                    window of implantation.
AUTHOR:             Kao L C; Tulac S; Lobo S; Imani B; Yang J P; Germeyer A;
                    Osteen K; Taylor R N; Lessey B A; Giudice L C
CORPORATE SOURCE:   Department of Gynecology and Obstetrics, Stanford
                    University, Stanford, California 94305, USA.
CONTRACT NUMBER:    U54 HD31398 (NICHD)
SOURCE:             Endocrinology, (2002 Jun) 143 (6) 2119-38.
                    Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200206
ENTRY DATE:         Entered STN: 20020522
                    Last Updated on STN: 20020619
                    Entered Medline: 20020618

L11  ANSWER 2 OF 3     MEDLINE on STN
ACCESSION NUMBER:   2002275003     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12015398
```

TITLE: Regulation of bone formation and vision by LRP5.
COMMENT: Comment on: N Engl J Med. 2002 May 16;346(20):1513-21. PubMed ID: 12015390
AUTHOR: Patel Millan S; Karsenty Gerard
SOURCE: New England journal of medicine, (2002 May 16) 346 (20) 1572-4.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Space Life Sciences
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020623
Entered Medline: 20020522

L11 ANSWER 3 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2002274995 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12015390
TITLE: High bone density due to a mutation in LDL-receptor-related protein 5.
COMMENT: Comment in: N Engl J Med. 2002 May 16;346(20):1572-4. PubMed ID: 12015398
Comment in: N Engl J Med. 2002 Sep 19;347(12):943-4; author reply 943-4. PubMed ID: 12239268
Comment in: N Engl J Med. 2002 Sep 19;347(12):943-4; author reply 943-4. PubMed ID: 12240686
Comment in: N Engl J Med. 2004 May 13;350(20):2096-9; author reply 2096-9. PubMed ID: 15141052
AUTHOR: Boyden Lynn M; Mao Junhao; Belsky Joseph; Mitzner Lyle; Farhi Anita; Mitnick Mary A; Wu Dianqing; Insogna Karl; Lifton Richard P
CORPORATE SOURCE: Department of Genetics, Yale University School of Medicine, New Haven, Connecticut 06510, USA.
CONTRACT NUMBER: AG15345 (NIA)
AR46032 (NIAMS)
CA85420 (NCI)
RR00125 (NCRR)
SOURCE: New England journal of medicine, (2002 May 16) 346 (20) 1513-21.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020926
Entered Medline: 20020522

=> d kwic 3

L11 ANSWER 3 OF 3 MEDLINE on STN
AB BACKGROUND: Osteoporosis is a major public health problem of largely unknown cause. Loss-of-function mutations in the gene for low-density lipoprotein receptor-related protein 5 (LRP5), which acts in the Wnt signaling pathway, have been shown to cause osteoporosis -pseudoglioma. METHODS: We performed genetic and biochemical analyses of a kindred with an autosomal dominant syndrome characterized by high bone density,. . . flies to humans. Markers of bone resorption were normal in the affected subjects, whereas markers of bone formation such as

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     osteocalcin were markedly elevated.  Levels of fibronectin, a
     known target of signaling by Wnt, a developmental protein, were also
     elevated.  In vitro studies showed that the normal inhibition of Wnt
     signaling by another protein, Dickkopf-1 (Dkk
     -1), was defective in the presence of LRP5V171 and that this
     resulted in increased signaling due to unopposed Wnt activity.
     CONCLUSIONS:.  .  .  LRP5 function in high bone mass and point to Dkk as a
     potential target for the prevention or treatment of osteoporosis
     .
CT   .  .  .
GE, genetics
      Case-Control Studies
      Chromosomes, Human, Pair 11
      Genes, Dominant
      Genotype
      Humans
      Mandible: PA, pathology
      Mandible: RA, radiography
      Mutation, Missense
        Osteogenesis: PH, physiology
      Palate: PA, pathology
      Pedigree
     *Point Mutation
      Proteins: PD, pharmacology
      Proto-Oncogene Proteins: AI, antagonists & inhibitors
     *Proto-Oncogene Proteins:.  .  .
CN   0 (Biological Markers); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0
     (Receptors, LDL); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (
     dkk1 protein, Xenopus); 0 (lipoprotein receptor related protein
     5); 0 (wnt8b protein, zebrafish)


=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1       446342 S BONE
L2          133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3           36 S L2 AND L1
L4           12 S L3 NOT PY>2002
L5            9 S L4 AND EXPRESS?
L6       211167 S OSTEO?
L7           24 S L2 AND L6
L8            9 S L5 NOT PY>2002
L9            7 S L8 NOT PY>2001
L10           0 S L7 NOT PY>2001
L11           3 S L7 NOT PY>2002

=> s lesion
        141659 LESION
        302187 LESIONS
L12     391994 LESION
                 (LESION OR LESIONS)

=> s l12 and l2
L13          5 L12 AND L2

=> s l13 not py>2002
       1489868 PY>2002
L14          0 L13 NOT PY>2002

=> d his
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     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1        446342 S BONE
L2           133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3            36 S L2 AND L1
L4            12 S L3 NOT PY>2002
L5             9 S L4 AND EXPRESS?
L6        211167 S OSTEO?
L7            24 S L2 AND L6
L8             9 S L5 NOT PY>2002
L9             7 S L8 NOT PY>2001
L10            0 S L7 NOT PY>2001
L11            3 S L7 NOT PY>2002
L12       391994 S LESION
L13            5 S L12 AND L2
L14            0 S L13 NOT PY>2002

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                     10.06      10.27

STN INTERNATIONAL LOGOFF AT 16:26:32 ON 25 JUL 2005
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